Sequencing of antineoplastic drug administration: contributions to evidence-based oncology nursing practice

Angelo Braga Mendonça¹, Eliane Ramos Pereira², Carinne Magnago³, Bruna Maiara Ferreira Barreto⁴, Ticiane Roberta Pinto Goes⁵, Rose Mary Costa Rosa Andrade Silva⁶

ABSTRACT
The objective of this study was to find scientific evidence of drug interactions between antineoplastic drugs that result from the administration sequence and then describe the best sequence and discuss its applicability to nursing care systematization (NCS). An integrative review of the literature was carried out in 2018 in the MEDLINE, LILACS, CINAHL, and BVS databases, with the terms neoplasms, drug Therapy, drug Interactions, chemotherapy, and sequence of administration. Fifty-seven studies were analyzed, which, as a set, studied 40 combinations of antineoplastic drugs and found pharmacokinetic and pharmacodynamic interactions resulting from the sequence of administration, which supported the construction of a chart that indicates the best sequence for each of those combinations. Along with the chart, a flowchart was also made to support NCS in the context of evidence-based oncology nursing practice. Selecting the sequences of antineoplastic drug administration is a new conceptual strategy designed for nurses who carry out multidrug therapy.

Descriptors: Drug Therapy, Combination; Drug Interactions; Neoplasms; Oncology Nursing.

¹ Nurse. Student in the graduate program in nursing at the Fluminense Federal University, master’s level. Nurse at the National Cancer Institute, Rio de Janeiro, RJ, Brazil. Email: angeloprimax@gmail.com.
² Nurse and psychologist, PhD in nursing. Associate professor at the Fluminense Federal University, Rio de Janeiro, RJ, Brazil. Email: elianeramos.uff@gmail.com.
³ Nurse, PhD in collective health. Guest professor, Rio de Janeiro State University, Rio de Janeiro, RJ, Brazil. Email: carinne.mag@gmail.com.
⁴ Nurse, PhD in health care sciences. Guest professor in the Hospital Pharmacy Residence course at the Fluminense Federal University, Rio de Janeiro, RJ, Brazil. Email: bruna.barreto07@gmail.com.
⁵ Nurse, master’s in nursing. Nurse at the National Cancer Institute, Rio de Janeiro, RJ, Brazil. Email: ticypinto@gmail.com.
⁶ Nurse and psychologist, PhD in nursing and PhD in social psychology. Associate professor at the Fluminense Federal University. Niterói, RJ, Brazil. Email: roserosauff@gmail.com.

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INTRODUCTION

Antineoplastic drugs are a major class of medicines used to fight cancer. Because of their complex administration, it is recommended that only qualified nurses\(^1\) administer them, since their evidence-based practice can properly handle the therapeutic and toxic effects of the treatment by means of a proper sequence of administration.

Since they are subject to the same pharmacokinetic and pharmacodynamic principles as any drug, antineoplastic agents have the same potential with regard to drug interactions. Considering that chemotherapy schemes generally use two or more drugs, the chances of interactions taking place get worse the higher the number of prescribed drugs is. Many of these interactions have significant clinical importance, since they can be minimally detrimental or sometimes even desirable. On the other hand, other interactions can have severe adverse effects, accounting for the death of about 4% of cancer patients.\(^2,3\)

For a long time, antineoplastic drugs with different actions have been combined with the purpose of overcoming drug resistance and increasing the dose and density of cytostatics. However, studies on the mechanisms through which cells enter and carry on the division cycle have contributed to a better association of drugs in current chemotherapy protocols. The acknowledgment of several checkpoints responsible for regulating the cell cycle allowed for an improvement of the clinical efficiency of therapeutic treatments and made it evident that the sequence of drug administration can maximize therapeutic effects without increasing clinical toxicity. These effects can be explained by cell cycle disturbances provoked by chemotherapy or by pharmacodynamic interactions between combined agents.\(^4\)

In that sense, and considering that most adverse drug interactions can be avoided with adequate planning of the infusion order, it is essential to study, assess, and acknowledge them so as to reduce mistakes, morbimortality, and costs related to iatrogenesis. A recent study on increasing cancer patient safety in chemotherapy showed the efficiency of multiprofessional interventions that protect patients, such as the implementation of a bar code prior to the administration of cytostatics, electronic prescriptions, pharmaceutical checks, the use of standardized drugs, and a manual of drug interactions to avoid mistakes in the administration sequence.\(^5\)

Despite the consistency of published results that support the administration sequence of certain protocols, there is a lack of data that provide good levels of evidence for others, especially those that include more recent drugs that are not usually used in practice. In the analysis of synergy, antagonism, and therapeutic and toxic effects, the results remain controversial for many combinations of cytostatics, and clarification by means of scientific evidence is needed.

The Oncology Nurse Society (ONS), the body that defines safety rules for chemotherapy administration, still does not have specific guidelines for the administration of antineoplastics, but it highlights the importance of creating institutional protocols and care standards that provide excellent care services.\(^6\)

In view of the above, and to support clinical decision-making, the objective of this study was to find scientific evidence on interactions between antineoplastic drugs that result from the sequence of administration and then describe the best sequence and discuss its applicability to nursing care systematization (NCS).
METHOD

This is an integrative review of the literature carried out in six steps: (1) formulation of the study question; (2) definition of the procedures for searching for evidence; (3) data collection; (4) data analysis; (5) critical analysis and interpretation; and (6) summary and presentation of results.

This review aimed at answering the following question: “What are the interactions between antineoplastic drugs resulting from administration sequence?” The inclusion criteria were primary studies that addressed antineoplastic drug interactions, resulting from administration sequence, that were approved for human use in Brazil by the National Health Surveillance Agency, and that were published in Portuguese, English, or Spanish. Publications without a clear and reproducible methodology were excluded, as were those found in more than one database and those that addressed the sequence of oncology protocols and not the sequence of drugs.

Between January 18 and February 28, 2018, the databases Medical Literature Analysis and Retrieval System Online (MEDLINE), via PubMed; the Health Virtual Library (BVS, per its acronym in Portuguese); the Cumulative Index of Nursing and Allied Health (CINAHL); and Latin American Caribbean Literature on Health Sciences (LILACS) were scanned, without a definite time frame. Other studies were included by means of cross-reference.

To define the method of search and identification of descriptors, a PIO strategy was adopted: (P) Population/problem = neoplasia; (I) Intervention = administration of antineoplastic drugs; and (O) Outcomes = synergistic interactions resulting from the administration sequence. The selected descriptors and MeSH were neoplasms, drug therapy, and drug interactions. The keywords chemotherapy and sequence of administration were also used. The terms were articulated by means of Boolean operators OR and AND.

The selection of publications was made in three steps. At the sorting stage, filters were applied to the databases in order to exclude unwanted studies, and afterward, duplicated studies. At the eligibility stage, inclusion and exclusion criteria were applied after reading titles and abstracts; at the inclusion stage, entire texts were read by two independent reviewers who agreed upon the inclusion or exclusion of the material selected at the previous stage, and the final sample was eventually determined. The included publications were then analyzed, summarized, and discussed in view of the proposed objectives.

RESULTS AND DISCUSSION

The searches found 1,034 publications, 57 (5.5%) of which made the final sample (Figure 1).

Figure 1: Flowchart of the selection process of scientific literature.
The 57 studies were published in English, in international journals, between 1973 and 2013, with the highest number of publications in 2001 (n = 6). Most of them were published in pharmaceutical and oncology journals, among which were the *Journal of Clinical Oncology* (24.6%) and *Cancer Chemotherapy and Pharmacology* (14%). There was no dissemination of the topic in nursing journals, which suggests the need to associate pharmacokinetic and pharmacodynamic studies with drug administration practices, since avoiding undesirable interactions by means of an adequate sequence is a technical and legal competence of nurses.

As for the method used to identify interactions, 27 studies (47.4%) carried out in vitro trials, which are defined as poor evidence to support specific recommendations. The significant number of interactions documented in these studies, which show synergy and antagonism resulting from the administration sequence, points to the need for investigation of the effects of a sequencing in clearly outlined clinical trials.

The pharmacokinetic and pharmacodynamic reasons for sequencing antineoplastic drugs and the clinical impacts observed are presented in Chart 1, which can be made available for use in treatment centers as an instrument to support decision-making.
<table>
<thead>
<tr>
<th>Administration:</th>
<th>Pharmacokinetic, pharmacodynamic, and clinical reasons for sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chart 1:</td>
<td>Administration sequence recommended for antineoplastic combinations with the respective pharmacokinetic, pharmacodynamic, and clinical reasons.</td>
</tr>
</tbody>
</table>
The reverse sequence causes a decrease of 50% in TXT clearance; lower potential synergism, whereas in the reverse sequence there is lower cytotoxicity. BLEO can block the progress of cell cycle at stage G2/M of tumor cells. CDDP significantly improves the antitumor efficacy of chemotherapy. Greater induction of apoptosis and inhibition of tumor cell growth. The administration of FAMP before ARA reduces the proportion of cells at stage S, hampering the antitumor effects of 5-Fluorouracil. The reverse sequence results in a lower TS inhibition than the DNA synthesis inhibition that occurs regardless of the PXT administration lasting 3 or 24 hours. However, the decrease in PXT cytotoxicity is not observed when the drugs are administered with a 48-hour interval or up to 24 hours. Antagonistic effect if administered 24 hours before or simultaneously. There is a possible competition between taxanes and anthracyclines mediated by P-gp. The pharmacokinetic interactions between PXT and ADM are responsible for the increase of ADM systemic exposure and its metabolite, doxorubicin, and the decrease in ADM clearance. Pretreatment with CPT remarkably increases ADM concentrations at the end of administration, therefore it reduces the creation of cleavage complexes in broken DNA chains, and its concentration in tumor tissues is greater in tissues pretreated with CPT than in tissues pretreated with ADM. The reverse sequence results in a lower TS inhibition than the DNA synthesis inhibition that occurs regardless of the PXT administration lasting 3 or 24 hours. However, the decrease in PXT cytotoxicity is not observed when the drugs are administered with a 48-hour interval or up to 24 hours. Antagonistic effect if administered 24 hours before or simultaneously. There is a possible competition between taxanes and anthracyclines mediated by P-gp.
### Administration sequence

**Pharmacokinetic, pharmacodynamic, and clinical reasons for sequencing**

LoE*

<table>
<thead>
<tr>
<th><strong>Sequence</strong></th>
<th><strong>Pharmacokinetic Reason</strong></th>
<th><strong>Pharmacodynamic Reason</strong></th>
<th><strong>Clinical Reason</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11/FU</td>
<td>Decrease in the AUC of SN38 metabolite</td>
<td>Synergy, with clear antiproliferative effects that depend on this sequence</td>
<td>(46) - (48)</td>
</tr>
<tr>
<td>CPT-11/FU</td>
<td>Increase of stage S cells</td>
<td>-</td>
<td>(47)</td>
</tr>
<tr>
<td>GEM/NVB</td>
<td>GEM can influence deamination of GEM to dFdU through deoxycytidine deaminase found in the liver</td>
<td>-</td>
<td>(50)</td>
</tr>
<tr>
<td>TPT/CDDP</td>
<td>Sequence CDDP-TPT induced significantly higher neutropenia and thrombocytopenia than the reverse sequence</td>
<td>-</td>
<td>(51)</td>
</tr>
<tr>
<td>TPT/DTX</td>
<td>Decrease in neutropenia</td>
<td>-</td>
<td>(45)</td>
</tr>
<tr>
<td>GEM/CDDP</td>
<td>Sequence GEM-CDDP has a higher apoptosis rate, with more cells blocked at stages G1 and S of the cell cycle</td>
<td>-</td>
<td>(53)</td>
</tr>
<tr>
<td>TPT-OXA</td>
<td>Decrease in neutropenia</td>
<td>-</td>
<td>(14)</td>
</tr>
<tr>
<td>TPT/CBDCA</td>
<td>Lower myelotoxicity, but CDDP clearance do not depend on administration sequence</td>
<td>-</td>
<td>(56)</td>
</tr>
</tbody>
</table>

**MTA:** Pemetrexed, **DTX:** Docetaxel, **PTX:** Paclitaxel, **GEM:** Gemcitabine, **5-FU:** Fluorouracil, **MTX:** Methotrexate, **OXA:** Oxaliplatin, **CBDCA:** Carboplatin, **NVB:** Vinorelbine, **CPT-11:** Irinotecan, **EPI:** Epirubicin, **VCR:** Vincristine, **CDDP:** Cisplatin, **CTX:** Cyclophosphamide, **IFO:** Ifosfamide, **VP-16:** Etoposide, **TDX:** Raltitrexed, **HER2:** Trastuzumab, **ARA-C:** Cytarabine, **LDP-341:** Bortezomib, **DHAQ:** Mitoxantrone, **FAMP:** Fludarabine, **BLEO:** Bleomycin, **CETUX:** Cetuximab. **AUC:** Area under the curve, **TFT:** Tophaceous, **TS:** Thymidylate synthase.
For six combinations of antineoplastic drugs, some studies did not find differences in pharmacokinetic profiles that depended on administration order (Chart 2).

**Chart 2**: Combinations of antineoplastic drugs without pharmacokinetic interactions that depend on administration order, as shown by some studies. Brazil, 2018

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXA-CPT11(P)</td>
<td>No pharmacokinetic interactions were detected between these agents. The main toxicities were neutropenia and late diarrhea, regardless of administration order.</td>
</tr>
<tr>
<td>GEM-OXA(P)</td>
<td>The sequences GEM-OXA and OXA-GEM showed a similar pharmacokinetic pattern, with no sequence-depending interaction.</td>
</tr>
<tr>
<td>PTX-CBDCA(P)</td>
<td>Carboplatin pharmacokinetics were not altered by PXT pretreatment with the standard dose. Pharmacokinetic interaction is not responsible for the lower toxicity of the combination. Neutropenia is the main effect, anemia is frequent, and thrombocytopenia has a lower incidence.</td>
</tr>
<tr>
<td>BEVA-CPT-11</td>
<td>BEVA does not affect CPT-11 pharmacokinetics. A variety of pharmacogenetic relationships can have an influence on CPT-11 pharmacokinetics and its toxicity.</td>
</tr>
<tr>
<td>CDDP-CPT-11</td>
<td>No pharmacokinetic changes are the result of administration order. This combination provides a practical and well-tolerated regimen, with potential synergy enhancement between agents.</td>
</tr>
<tr>
<td>ADM-PTX</td>
<td>The administration order does not affect pharmacokinetics and toxicity. High complete response rates and congestive heart failure are the expression of therapeutic and toxic effects of this combination.</td>
</tr>
</tbody>
</table>


For the sequences bevacizumab-irinotecan (BEVA-CPT-11), cisplatin-irinotecan (CDDP-CPT-11), oxaliplatin-irinotecan (OXA-CPT-11), and paclitaxel-carboplatin (PXT-CBDCA), there were no clinical effects in terms of toxicity or therapeutic benefits. As for the sequence PXT-CBDCA, although this study did not find scientific evidence to support it, the literature strongly recommends this order. The justifications are based on the risk of neutropenia caused by platin analogues when they precede taxanes in the sequence, and on the risk of lesions secondary to extravasation of vesicant agents, such as PXT.

Controversial results for the sequence doxorubicin-paclitaxel (ADM-PXT) (Charts 1 and 2) are partly due to the small sample size and to the genetic variability observed among individuals. Genetic polymorphisms are responsible for the diversity of the load of inducing and metabolizing enzymes and influx carriers, resulting in different responses and degrees of interaction between drugs. It has been suggested that genetic factors can contribute to 20–95% of the variability of the therapeutic and toxic efficiency of ADM. Therefore, the understanding of ADM metabolic pathways has demonstrated pharmacogenetic, pharmacokinetic, and pharmacodynamic correlations, favoring therapy individualization. Likewise, some studies have shown that longer ADM infusion times may not only result in changes of pharmacokinetic standards but also in cardiotoxicity, which conflicts with the results of the analyzed studies. In this context, pharmacokinetic interactions with the combination were best described in studies with PXT administered for 24 hours instead of 3 hours. The reviewed publications that advocated for the sequence ADM-PXT were clearly better than those that suggested a lack of interaction for the sequence. Given the importance and consequences of a rise in plasma concentrations of doxorubicin, this article recommends ADM-PXT.

For the sequence gemcitabine-oxaliplatin (GEM-OXA), favorable in vitro results (Chart 1) did not bring better clinical in vivo benefits (Chart 2), reinforcing the need for caution in its interpretation and practical use.

**DISCUSSION**

Administering chemotherapy in the wrong order is considered a medication error, and it is the most common cause of error (50.5%) among nurses who work in outpatient chemotherapy centers.\(^\text{[73]}\) This finding confirms the relevance of planning the infusion order on the basis of good levels of evidence to support decision-making, as recommended by evidence-based practice (EBP).

With the purpose of guiding the administration sequence performed by nurses, according to EBP, a flowchart is presented in Figure 2.

**Figure 2**: Flowchart of support to evidence-based practice of the administration sequence of antineoplastic drugs Brazil, 2018.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the primary study that gave rise to the protocol present the infusion order?</td>
<td>Follow the order recommended by the protocol that gave rise to the study.</td>
<td>Keep the recommended order.</td>
</tr>
<tr>
<td>Is the sequence supported by a randomized clinical trial that confirms the benefits and risks of the sequence?</td>
<td>Keep recommendation.</td>
<td>Use caution when following the recommendation!</td>
</tr>
<tr>
<td>Although the study which analyzed the sequence is not randomized, does it assess the results with the reverse sequence, clearly showing the risks and benefits?</td>
<td>Use caution when following the order!</td>
<td>Administer vesicant agents first. If the protocol includes a drug with a high potential for a hypersensitive response, it must be administered last, since in the case of a severe reaction, treatment is interrupted and patients are not given the other drugs in the sequence.</td>
</tr>
<tr>
<td>Was the study which analyzed the interaction results carried out with murinae or other animals?</td>
<td>Use caution when following the recommendation!</td>
<td>Use caution when following the order!</td>
</tr>
<tr>
<td>Did the study which analyzed the sequence provide results of in vitro interaction?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are pharmacokinetic and pharmacodynamic interactions absent in the sequence?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The antineoplastic sequence chart must be assessed along with the flowchart (Figure 2), since certain chemotherapy protocols already define the sequence and infusion length of drugs. They are enshrined because they come from stage III or IV multicenter studies and follow large populations of patients for a long time. Changes in their flow can hinder treatment effectiveness in terms of clinical benefits, overall survival, and safety.

To reduce the risks of a change in the sequence laid down in chemotherapy protocols, publications, such as oncology manuals and handbooks, containing a precise description of the regimen must be checked before the administration of drugs. If the order is not explicit for the concerned regimen, nurses are responsible for clarifying...
the sequence as part of the nursing process. To do so, a nursing verification process is recommended through which expert nurses double-check the antineoplastic prescriptions, by checking the correct combination of drugs and calculating the body surface, the interval between cycles, the dose adequacy, the dilution standard, and the order and length of infusion.\(^{(74)}\)

In the absence of pharmacokinetic and pharmacodynamic interactions, the literature recommends the administration of vesicant agents before nonvesicants in peripheral veins, as shown in the flowchart (Figure 2). This strategy reduces the risk of extravasation, since at the beginning of treatment, vessels are intact, that is, less affected by local reactions induced by other agents, such as erythema, pain, and pruritus.\(^{(75)}\) When it comes to combinations with more than one vesicant agent, the risks and severity of lesions secondary to extravasation\(^{(76-77)}\) justify the administration of vesicant agents, which bind to the DNA first, followed by those that do not bind, and finally, neutral chemotherapy drugs.

Although the best evidence available was analyzed so that Chart 1 could be made, it is worth mentioning that up to now, no systematic reviews and meta-analyses of antineoplastic drug infusion order were found, and such studies are considered to be of greater relevance for clinical decision-making, according to EBP.

With regard to evidence strength of in vitro studies, many of them analyzed the effect of the sequence of antineoplastic drugs through incubation of cell lines in drugs for 24 hours or longer. These results may not be consistent in supporting the practice of sequencing drugs administered on the same day in human beings. Despite strong evidence of effects on cell cycle induced by infusion order shown in these studies, the drug pharmacological action profile may vary significantly given the changes in pharmacokinetic patterns observed in vivo. Among these patterns, we can mention the plasma protein binding of the drug, and its distribution, metabolism, clearance, half-life, and action time in the body.

Studies with in vivo drug interactions that showed changes in pharmacokinetic patterns have major clinical relevance, since they determine with greater precision drug concentration in different body parts, the time it takes to get to the site, the duration and extent of the therapeutic/toxic effects, and time to clear.

Although in vitro studies can have limitations in supporting a given sequence in nurses’ clinical practice, in the absence of in vivo interactions and when it comes to neutral agents (with no vesicant or irritant nature), they can provide a reasonable justification when determining infusion order. The findings of this type of study have important implications to the design of current chemotherapy protocols, since they provide important molecular information about the effects of drug interaction at a cellular level. Their careful review shows a large number of in vivo substrates for antineoplastic drugs, enzymatic inhibitors and inducers, responsible for metabolism and drug interactions\(^{(78)}\).

In vitro methods are increasingly progressing with 3-D cell culture. In addition to the toxicity analysis related to drugs, they have a special importance in the assessment of drug administration strategies, with great potential in terms of specificity in target-driven therapy, drug interactions at cellular level, and the role of excipients in interactions. These new models offer the possibility to investigate advanced treatments, including genetic drugs and formulas with nanoparticles, and they promise consistent results in terms of sensitivity to drugs and toxic effects. Among the challenges to come, we can mention stronger in vitro-in vivo correlations to improve reliability and ensure safe use.\(^{(79)}\)
In vitro studies therefore have value and cannot be ruled out for decision-making purposes. The lack of high-quality evidence for some antineoplastic drug sequences does not prevent EBP decision-making. In this situation, it is the best evidence available that is required, not the best evidence possible.\(^{(80)}\)

The great variability and complexity of combinations of drugs and ongoing clinical regimens, in addition to a quick adoption of research protocols in conventional clinical treatments, have required a frequent retraining of doctors, nurses, and chemists in the search for better evidence.

**Implications for Nursing Care Systematization**

The most frequent negative effects found in sequence-dependent in vivo studies in this review were neutropenia\(^{(18,25,28,30,33,45,51,56)}\) and thrombocytopenia,\(^{(51,56)}\) which are closely related to nursing diagnosis of “risk of infection” and “risk of bleeding.” Other toxic effects involved in the administration order were diarrhea,\(^{(49)}\) hepatotoxicity,\(^{(50)}\) nausea,\(^{(49)}\) vomiting,\(^{(56)}\) mucositis,\(^{(33)}\) and cardiotoxicity,\(^{(34)}\) which are also associated with nursing diagnosis, as provided for in the NANDA International classification system.\(^{(81)}\)

In outpatient oncology services, care provided must focus on individuals’ needs, with the help of nursing diagnoses as a standardized taxonomy. This tool provides support for decision-making and guides the choice of interventions that are more efficient in order to improve patients’ response to antineoplastic treatments.\(^{(82)}\)

A study that analyzed the nature and classification of nursing interventions in an adult chemotherapy outpatient facility found a predominance of actions aimed at nutritional advice, with no reports of nursing diagnoses of “risk of infection,” nor interventions for its prevention/control and planning of drug administration order.\(^{(83)}\) These findings are noteworthy, since this shortcoming increases patients’ vulnerability to infectious complications, in addition to other effects resulting from errors in drug administration order. By means of effective planning of the infusion order, nurses can, in their practice, not only reduce the incidence and severity of these complications but also adjust doses and delays in treatment caused by severe and long-term myelosuppression.

Therefore, the nurse who administers antineoplastic chemotherapy is responsible for supervising and guiding care aimed at prevention of infections. Such interventions must be planned at the third stage of the nursing process,\(^{(84)}\) considering the specific myelotoxic potential of the drugs, the time of nadir, and bone marrow recovery for the concerned protocol.\(^{(85)}\) At the fourth stage of the nursing process, called the assistance implementation stage (nursing prescription),\(^{(84)}\) some studies have prioritized interventions in elderly patients, patients with breast cancer and high-grade hematologic neoplasia, the control of neutrophil counting, prophylactic administration of hematopoietic growth factors,\(^{(85)}\) and chemotherapy drug infusion, following an order that reduces the risks of febrile neutropenia. The last intervention is capable of providing the best therapeutic response, which comes from the biochemical and pharmacodynamic synergy between the agents involved in the sequence.

In view of the above, the planning of the infusion order must be done with the same thoroughness with which the device for vascular access is chosen and the catheter is inserted. Such actions are aimed at preventing skin lesions secondary to extravasation and reducing toxic effects resulting from an inadequate sequencing.
Recommendations to improve safety and reduce errors in chemotherapy administration include the implementation of standardized processes and strict compliance with policies and routine procedures, with the purpose of ensuring quality at all stages of the process.\cite{6,74}

In this context, the antineoplastic drug sequence chart (Chart 1) can support the definition of standards for the infusion order and consequently improve the effectiveness of chemists and nurses by reducing waiting time in chemotherapy outpatient facilities with a high number of patients, avoid the preparation of drugs that will not be administered in the first place, and reduce the risks of errors resulting from wrong sequencing, drug skipping, protocol violation, and delays in treatment.

To improve patient safety, staff must be aware of the same information and carry out the same conduct regarding the clinical implications of the infusion order. The awareness of risks involved in this nursing action demonstrates the need for managers to highlight best practices when they create institutional protocols for cytostatic drug administration, which is part of NCS. In view of this new reality, it should be noted that an incorrect sequence of antineoplastic drugs is a risk to the physical integrity and survival of patients undergoing chemotherapy, and it requires the presence of highly skilled nursing professionals who are aware of evidence-based knowledge of the nursing process.\cite{85}

CONCLUSIONS

The administration of chemotherapy and its duration require a deep knowledge by nurses of its molecular, pharmacodynamic, and pharmacokinetic mechanisms. Selecting the sequences of combined antineoplastic drug administration, on the basis of these mechanisms, is a new conceptual strategy designed for nurses who carry out multidrug therapy.

The chart created in this study, which indicates the best sequences, is an instrument that can be easily consulted by nurses and chemists, and it can be made available for infusion services in order to contribute to the prevention or reduction of errors arising from an inappropriate infusion sequence. It aims to ensure lower toxicity and greater clinical benefits to patients as the result of a better synergistic interaction between drugs. In that sense, it is an important tool for NCS, which supports the management of risks for a safer care.

It is worth mentioning that a limitation of this study concerns the absence of studies with high levels of evidence capable of gathering the administration sequences for the main protocols used in clinical practice. Likewise, there are few studies that address NCS in the context of multidrug therapy. In view of the above, new studies that fill these knowledge gaps are necessary to support EBP and therefore ensure safer and more efficient care.

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